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Authors
Lukowsky, Lilia R
Kheifets, Leeka
Arah, Onyebuchi A
et al.

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Patterns and Predictors of Early Mortality in Incident Hemodialysis Patients: New Insights

Lilia R Lukowsky, MPH[1,2], **Leeka Kheifets, PhD**[2], **Onyebuchi A Arah, MD, PhD**[2,3], **Allen R Nissenson, MD**[4,5], and **Kamyar Kalantar-Zadeh, MD,MPH, PhD**[1,2,4]

[1]Harold Simmons Center for Chronic Disease Research & Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA [2]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA [3]Department of Public Health, Academic Medical Center, University of Amsterdam, The Netherlands [4]David Geffen School of Medicine at UCLA, Los Angeles, CA [5]DaVita, Inc, El Segundo, CA

Abstract

Background—Incident hemodialysis patients have the highest mortality in the first several months after starting dialysis treatments. We hypothesized that the pattern and risk factors associated with this early mortality differ from those in later dialysis therapy periods.

Methods—We examined mortality patterns and predictors during the first several months of hemodialysis treatment in 18,707 incident patients since the first week of hemodialysis therapy and estimated the population attributable fractions for selected time periods in the first 24 months.

Results—The 18,707 incident hemodialysis patients were 45% women and 54% diabetics. The standardized mortality ratio (95% confidence interval) in the 1st to 3rd month of hemodialysis therapy were 1.81 (1.74-1.88), 1.79 (1.72-1.86), and 1.34 (1.27-1.40), respectively. SMR reached prevalent mortality only by 7th month. No survival advantage for African Americans existed in the first 6 months. Patients with low albumin <3.5 g/dL had the highest proportion of infection-related deaths while patients with higher albumin levels had higher CV deaths including76% of death during the first 3 months. Use of catheter as vascular access and hypoalbuminemia <3.5 g/dL explained 34% (17%-54%) and 33% (19%-45%) of all deaths in the first 90 days, respectively.

Conclusions—Incident hemodialysis patients have the highest mortality during the first 6 months including 80% higher death risk in the first 2 months. Presence of catheter and hypoalbuminemia<3.5 g/dL each explains 1/3 of all deaths in the first 90 days.

Keywords

Incident hemodialysis patients; mortality predictor; population attributable fraction

Correspondence: Kamyar Kalantar-Zadeh, MD PhD MPH, Harold Simmons Center for Chronic Disease, Division of Nephrology and Hypertension, Harbor-UCLA Medical Center, 1124 West Carson Street, C1-Annex, Torrance, CA 90509-2910, Phone: 310-222-3891, Fax: 310-782-1837, kamkal@ucla.edu.

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Potential Conflict of Interest:
None declared.

Introduction

The number of patients with end-stage renal disease (ESRD) in the United States has increased from about 60,000 in 1980 to over half a million in 2008.[1] It is projected that this number would surpass 800,000 by 2020.[2] These patients would not have survived without kidney transplantation or dialysis therapy, which currently comprises mostly of hemodialysis treatment in this country. However, dialysis patient mortality is unacceptably high, currently approximately 20% per year in the United States. Mortality appears to be even higher during the first year of dialysis therapy, especially in the first few months,[2] while factors contributing to early death are widely unknown.

The most common cause of death in dialysis patients is cardiovascular followed by infectious disease. In a recent study that examined the early mortality among incident hemodialysis patients during the first 120 days vs. subsequent 121 to 365,[3] cardiovascular causes were still the most common for the entire first year. Even though previous studies identified several important factors associated with elevated mortality among incident hemodialysis patients, few have addressed the risk factor patterns and their changes over time during the first few months of dialysis therapy. It is crucial to assess whether those risks remain constant or whether the risk patterns are altered over time, so that focused interventions can be used at different periods of time. Comorbidities including severity of kidney disease at the time of dialysis initiation could play an important role in survival of dialysis patients.[3] Several recent observational studies[4-6] and at least one randomized trial[7] have indicated that the higher glomerular filtration rate (GFR) at the time of dialysis initiation was associated with elevated mortality risk in dialysis patients, although this may be due to the fact that sicker and older patients start dialysis therapy earlier.[8] Use of central venous catheters (CVC), which exits in up to 82% patients at the start of hemodialysis therapy,[9-12] has been implicated as an important mortality predictor in several studies [9, 12].

We hypothesized that mortality rate is substantially higher during the first few months of dialysis initiation and that the risk factors associated with this high mortality are different from those in later periods of dialysis therapy. We examined the associations between the mortality and the putative risk factors during different time periods within the first 24 months after the start of hemodialysis therapy among a large group of incident hemodialysis patients who had started treatment at one of the DaVita dialysis facilities in the United States between 7/2001 and 6/2006 and whose clinical outcomes were followed during the 5-year period.

Methods

Sources of Data, Study Population and Follow-up

DaVita is one of the largest dialysis providers in United States. For this study we examined the cohort of all incident hemodialysis patients who started the first week of hemodialysis treatment from July 01, 2001, to June 30, 2006, at one of DaVita dialysis centers. Patients who used peritoneal dialysis modality at any given time were excluded. Information about

the date when patient entered the DaVita cohort, dialysis treatment modality, date when the first hemodialysis treatment started, demographic characteristics, co-morbidities, and laboratory and other clinical measures were collected at the time of the start of enrollment in DaVita. Using unique identifiers, data form DaVita and the United States Renal Data System (USRDS) databases were cross-linked to corroborate the information about dates of the events including death and transplantation, and co-morbidities at the start of dialysis therapy, dialysis modality and laboratory data prior to the dialysis treatment were verified as well.[13] To examine the patterns of survival in the first 2 years of hemodialysis treatment, the cohort time was divided into *a priori* selected smaller groups, i.e. <3 months, 3 to <6 months, 6 to <12 months, and 12 to 24 months. Patients were followed for up to 5 years (1,830 days) or until death, kidney transplantation, or the end of the follow-up. Person-time was obtained by calculating the difference between the dates when the first hemodialysis treatment started at one of the DaVita clinics and the end of follow-up or other censoring events.

Laboratory Parameters

All blood samples were drawn using standardized procedure and transported to the Central DaVita Laboratory located in Deland, FL usually within 24 hours. Blood or serum levels of albumin, creatinine, phosphorus, calcium, bicarbonate, total iron-binding capacity (TIBC), iron (transferrin) saturation ratio (ISAT or TSAT, i.e. iron divided by TIBC), white blood cells count (WBC), and lymphocyte counts were usually measured monthly. Serum ferritin was measured at least quarterly. Hemoglobin was measured weekly to biweekly. Estimate of prescribed dialysis treatment dose, known as Kt/V (single pool) [14] and protein intake known as normalized protein catabolic rate (nPCR)[15] were obtained using urea dynamic equations. All measurement were averaged over the first calendar quarter (up to 13 weeks) to calculate one single value for each laboratory parameter per each patient. Since most of these laboratory measurements (albumin, creatinine, phosphorus, calcium, bicarbonate, TIBC, WBC, lymphocyte, ferritin, and nPCR) and body mass index (BMI) may reflect the nutritional and/or inflammatory status of dialysis patients, they are referred to as the "malnutrition-inflammation cachexia syndrome" (MICS) throughout this study.[16]

In order to calculate summary estimates of the exposure variability as putative risk of death in a clinically relevant and commensurate format, we rescaled some laboratory measures by defining biologically and clinically meaningful increments including 0.2 g/dl of albumin, 0.2 g/kg/day of nPCR, 2 mEq/L of bicarbonate, 2 kg/m^2 of BMI, 10% of lymphocyte percentage, 100 pg/ml of PTH, 10% of ISAT, 50 mg/dl of TIBC, 500 ng/ml of ferretin, and 5×10^3/HPF of WBC. For other laboratory values, one conventional unit was used such as 1 mg/dL increase in serum calcium or phosphorus concentrations. Age was also examined as decades of increments. Additionally we also examined the associations between the mortality and clinically relevant dichotomies for selected laboratory variables including serum albumin (comparing mortality for patients with <3.5 g/dL vs. >=3.5 g/dL), hemoglobin (>=10 g/dL vs. <10 g/dL), and nPCR (>=1 g/kg/day vs. <1 g/kg/day).

Statistical Analyses

Descriptive analyses were conducted to examine the population characteristics across the *a priori* selected survival periods of <3 mo, 3-<6 mo, 6-<12 mo and 12-<24 mo. Estimated hazard functions were examined by the life table methods. Five-year unadjusted and adjusted survival curves using Kaplan-Meier (KM) estimation were produced for the entire population as well as for the important demographic characteristics and co-morbidities. Survival curves were adjusted for four main demographic features including age, gender, presence or absence of diabetes mellitus upon dialysis therapy and race, i.e. African Americans vs. others. We also calculated monthly *Standardized Mortality Ratios* (SMRs) for each of the first 24 months of dialysis treatment for the incident hemodialysis patients under the study. The rates were standardized to age, gender, diabetes status, and race using the cohort of all other patients who started hemodialysis treatment in a DaVita clinic within 90 days from dialysis initiation. Multivariate logistic regression models were fit in order to estimate the SMR for each month[17] Cox proportional hazard models were used to calculate hazard ratios of death at different time periods during the 24 months and for the 5-year survival for the patient characteristics including demographics, co-morbidities and laboratory values. For each selected period, deaths before and after the period were censored and the person time was limited to the given period.

Two levels of multivariate adjustments were used in most survival analyses: (A) *Case-mix and dialysis treatment adjusted models* which included adjustment for age, gender, four mutually exclusive race/ethnicity categories (African Americans, Hispanics, non-Hispanic whites, and others), primary insurance (Medicare, Medicaid, and other), marital status (married, single, divorced, widowed), dialysis vascular access, i.e., central venous catheter (CVC), arteriovenous fistula (AVF), or arteriovenous graft (AVG); dialysis dose (single pool Kt/V), diabetes mellitus as well as 11 additional co-morbid conditions including atherosclerosis, congestive heart failure (CHF), other cardiac conditions, cerebrovascular disease (CVA), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), cancer, hypertension, inability to ambulate, and smoking status; and entry calendar quarter for secular trend. (B) *Fully adjusted models*, which included adjusted all of the above, as well as 10 above-mentioned laboratory surrogates of the MICS and BMI. Some of the adjustors were also examined as independent predictors of death risk.

The *Population Attributable Fractions* (PAF)[18] were calculated for the relevant comorbidities and the CVC vascular access to assess the percent of deaths that could be attributable to those factors, and therefore, hypothetically preventable proportion by eliminating or reducing them. The 95% confidence interval for each PAF was calculated by the substitution method.[19] All the analyses were conducted by using SAS 9.2 software (SAS Inc., NC).

Results

From 1 July 2001 to 30 June 2006 a total of 82,566 incident (new) dialysis patients started chronic dialysis treatment in a DaVita dialysis clinic within the first 90 days of therapy initiation. After excluding patients younger than 18 years (n=637), incident peritoneal dialysis patients or those who switched modality at any given time (n=4,763), hemodialysis

patients with missing person-time (n=6) and hemodialysis patients who initiated the first week of dialysis therapy outside of a DaVita clinic (n=58,453, which served as the "reference" population to calculate SMRs, see above and below), a total of 18,707 incident hemodialysis patients who had never switched modality remained in the cohort. These patients had received at least one treatment of the first therapy week in a DaVita clinic and had remained in DaVita throughout the entire first 90 days or until death or transplantation.

During the first 24 months, 6,666 patients died (36% or 30 deaths per 100 person years) and 1,399 received a kidney transplant. **Table 1S** (on-line appendix) compares the baseline demographic, clinical and laboratory features of the entire 18,707 patents with the reference cohort of 58,453 patients. The overall probability of survival of these incident HD patients for 3 mo, 6 mo, 1 yr, 2 yrs, and 5 yrs were 0.90 (0.89-0.91), 0.80 (0.79-0.82), 0.72 (0.71-0.73), 0.58 (0.57-0.59), and 0.26 (0.25-0.27), respectively. **Figure 1** shows the monthly SMRs over the first 24 months after dialysis therapy initiation in 18,707 incident hemodialysis patients under the study using the cohort of other 58,453 incident hemodialysis patients (see above) as the reference population. The highest mortality occurred during Months 1 and 2, and mortality rates decreased over a period of 7 months. The calculated SMR (and 95% CL) for the 1st to 4th month of dialysis therapy were 1.81 (1.74-1.88), 1.79 (1.72-1.86), 1.34 (1.27-1.40) and 1.35 (1.28-1.41) respectively (see Figure 1).

Examining the distribution of 6,666 deaths in the first 24 mo, crude mortality rates during the 4 *a priori* selected periods of <3 mo, 3-<6 mo, 6-<12 mo, and 12-<24 mo were 1,994 (30% of all deaths or 47 deaths per 100 person-years), 1,271 (19% or 35 per 100 person-years), 1,550 (23% or 25 per 100 person-years), and 1,851 (28% or 22 per 100 person-years), respectively. **Table 1** shows the characteristics for the deceased patients across the 4 *a priori* selected mortality periods of <3 mo, 3-<6 mo, 6-<12 mo, and 12-<24 mo compared to >=24 mo survivors. Early death was associated with more advanced age, higher proportion of CVC, and higher prevalence of cardiovascular diseases. Those who died during the first 3 months had 1.9 co-morbidities per person compared to 1.1 among those who survived >=2 years. **Figure 2** shows the common kidney disease etiologies, i.e., ESRD diagnoses, among patients who died during each of the a priori selected periods of the first 24 months. Diabetes and hypertension were the 2 most common ESRD diagnoses; however, hypertension was more frequent among those with earlier deaths, whereas diabetes was more frequent among those who survived the earlier months. **Figure 3** shows the causes of death during the first 24 months. Nearly similar death cause distribution was noticed in the first 90 days indicating that half of all deaths were marked as cardiovascular. Mortality due to withdrawal from dialysis was the lowest during the first 90 days and rose over time from 2% to 8% in second year. **Table 2** shows case-mix adjusted death hazard ratios during the 4 survival periods. The known survival advantage of African American race was noticeable only after 6 months of therapy but not prior to that. Diabetes mellitus and lower nPCR were paradoxically associated with greater survival at early time periods but they were predictors of higher mortality during later periods.

In addition to all-cause mortality, we also examined the associations of cause-specific mortality, i.e., CV and infection-related deaths, with race (non-Hispanic whites, African Americans and Hispanics), history of CHF, CVC vascular access and hypoalbuminemia as

presented in **Table 3**. Compared to Whites, both African Americans and Hispanics showed slightly better survival in terms of CV and infection-related mortality, although the associations were uncertain initially. Of note, patients with CHF showed elevated risk of death independently of the cause of death. Moreover the associations were higher for both CV (1.68 [1.41-1.99] during the first quarter) and infection related deaths (1.56 [1.14-2.14] during the first quarter) comparing to all-cause mortality (1.31 [1.11-1.54]). Use of CVC access was associated with the deaths from infections much stronger (3.32 [2.14-5.16] during the 1st quarter) comparing to CV deaths. Similarly, low serum albumin levels were associated with the infection related mortality much stronger (4.92 [3.45-7.00] in the first 3 months) than with CV mortality during the same time period.

Table 2S (online appendix) shows selected Population Attributable Fractions including for vascular access and co-morbidities. CVC as the dialysis access could explain 34% of all deaths in the first 3 months of dialysis therapy. A low serum albumin<3.5 g/dL had a similar death contribution, i.e., 33% of deaths in the first 90 days could have been prevented if albumin levels were above 3.5 g/dL.

Discussion

Examining the mortality pattern during the first 24 months of a contemporary (2001-2006) and nationally representative cohort of 18,707 incident hemodialysis patients who received treatment from the first week of hemodialysis therapy in a DaVita dialysis clinic, we found that mortality was exceptionally high in the first 6 months, especially during Months 1 and 2 with an SMR of 1.81 and 1.79, respectively, compared to all incident hemodialysis patients of the same cohort period. We also assessed the risk of death during different time periods to identify modifiable risk factors and their contributions to death over time and found that use of CVC as the vascular access and hypoalbuminemia <3.5 mg/dL could explain 34% and 33% of all deaths in the first 90 days, respectively. These novel findings may have important clinical and public health implications, since they may offer impetus for designing interventions and trials to reduce early death among incident dialysis patients. We found that both all-cause and cardiovascular mortality rates were the highest during the first 2 months of dialysis therapy, which is consistent with several previous reports [3, 12]. Among demographic predictors of death, older age, white race, Medicaid coverage, and being single or widowed were also associated with higher death risk in the first 24 months.

Worse survival of non-Hispanic white dialysis patients is consistent with previous reports [3, 20]. Even though it is remains unclear as to why African Americans have lower dialysis mortality risk, in our study the survival advantage of African Americans or other minorities was almost non-existent in the first 6 months. Of note, the racial distribution of patients who died within the first 3 months consists of 62% non-Hispanic whites, 20% blacks and 12% Hispanics in contrast to the 47% whites, 27% blacks, and 15% Hispanics among survivors over 2 years (Table 1), which is consistent with the survival advantage of minorities [21]. However, after case-mix adjustment advantage for African Americans during early dialysis period disappeared. Similar to all-cause mortality African Americans exhibited essentially the same pattern with CV mortality with practically no survival advantage over whites in the early time periods, although a somewhat better survival in infection related morality. The

observation that African Americans had somewhat lower CVC use than whites (data not shown) might explain the higher infection-related mortality in whites. Hispanics, too, showed better survival in infectious deaths analyses; however, although whites had somewhat higher percentage of CHF history, Hispanics contributed to a higher percentage of patients with low serum albumin levels and CVC use similar to whites. Both hypoalbuminemia and CVC access are known to be associated with infectious events and death. It might be that, while Hispanics were more likely to develop infections, they may be less likely to die from them. Another explanation as to why Hispanics and, to some extent, African Americans had higher rates of hypoalbuminemia but lower infection-related mortality could be that, for most of the minorities, low albumin levels may be more indicative of malnutrition than infection [22].

An interesting finding was the seemingly paradoxical association between diabetes and lower mortality in the first months, which was previously reported by Bradbury et al [3]. The possible explanation may be that they were more likely to see a physician on regular basis compared to non-diabetics and therefore may have been better prepared for the transitional period of early dialysis therapy. However, this survival advantage mitigated and even reversed over time probably because non-diabetics who survived the transitional period might be healthier than patients with diabetes.

Among clinical predictors, type of the vascular access was exceptionally strongly associated with mortality across all studied periods but in particular during the first 90 days, including both among CV and infection related deaths. Although our finding was consistent with previous reports indicating that CVC was associated with higher mortality in hemodialysis patients [9-12], our study uniquely shows that the association of vascular access type with mortality is the strongest at the time of dialysis initiation and decreased over time, which suggests the importance of replacing CVC with a more permanent access within the first few weeks – if not days – of dialysis therapy. Our results are consistent with findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) reporting higher mortality for patients with CVC access comparing to other types. That study found that US patients had 36% to 43% higher mortality risk due to wide spread use of CVC use compared to European countries and about 30% higher when compared to Japan [23].

The resilient role of low serum albumin level in predicting high mortality of dialysis patient has been previously identified;[3, 24, 25] this is verified in our current study. A 10-year cohort study from Japan reported that patients with serum albumin levels >3.8 g/dL consistently had better survival [24]. We found 21% increase in mortality in the first 90 days per 0.2 g/dl lower serum albumin compared to 12% during the 12-24 month period. We found that infection-related and CV mortality rates were respectively 5-fold and 2-fold higher among patients with low serum albumin levels <3.5 g/dl compared to higher levels. We also found that, among patients with no history of CHF and hypoalbuminemia, the percentage of deaths related to infections was the highest especially during the first 6 months on dialysis (19% to 21%), while patients with history of CHF and serum albumin >3.5 g/dl accounted for only 8% of infection-related deaths in the first 3 months of dialysis treatment (Table 3). Although hypoalbuminemia was strongly associated with both CV and infection-related mortality, it seems that, among patients who died from CV disease, CHF,

which is usually due to volume overload, could be responsible for the patient outcomes especially during the early months of the dialysis treatment. Patients with CHF have higher CV mortality than patients without it, and the highest CV mortality of 76% was observed during the first 3 months of dialysis treatment in patients with CHF and serum albumin >3.5g/dl.

In a recent study from UK Renal National Registry cohort , using several models for predicting the first 3-year survival of incident dialysis patients, older age, white race, diabetes mellitus and other primary causes of ESRD, history of cardiovascular disease and smoking were predictive of increased mortality [27]. Among laboratory parameters, serum levels of albumin, hemoglobin, and calcium were also predictors of 2-year mortality [27]. These findings are somewhat similar to our results.

Our study should be qualified for including only DaVita patients rather than the entire national dialysis population. However, DaVita patients are likely good representatives of average ESRD patients. We purposely excluded the incident patients who initiated their first week of therapy elsewhere to mitigate selection bias. It can be argued that there could be differences between the patients who started dialysis at an inpatient vs. outpatient facility. Nevertheless, the annualized mortality in our cohort for the first 3 months was about 30%, which was consistent with mortality reported for US patients in the same period [2]. We had no reliable information about patient visiting nephrologists prior to dialysis initiation (80% missing values), which precluded examination of this potential predictor of early mortality.

Conclusion

Incident hemodialysis patients have the highest mortality during the first 6 months of dialysis therapy, in particular in the first 2 months, and cardiovascular disease is the most common causes of death. Use of CVC as vascular access and hypoalbuminemia <3.5 mg/dL each explains 1/3 of all deaths in the first 90 days. Hence, replacing or avoiding CVC and improving hypolabuminemia could theoretically reduce early dialysis death by 30%. These findings warrant imminent design of clinical trials to examine interventions to target imminent AV fistula placement and to increase serum albumin in order to reduce early death among incident dialysis patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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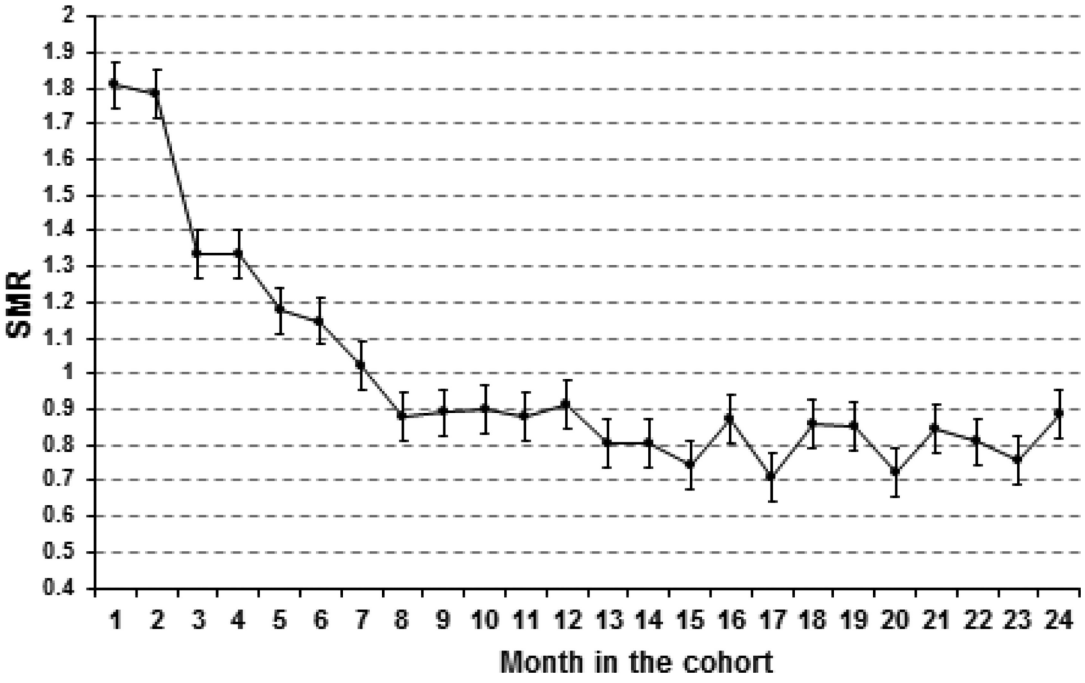

Figure 1.

Monthly standardized mortality ratios (SMRs) during the first 2 years for the incident dialysis pts (n=18,707). SMRs are standardized by age, gender, diabetes and race using the reference cohort of 57,456 hemodialysis patients who started DaVita cohort within 30 days after starting dialysis treatment (see text)

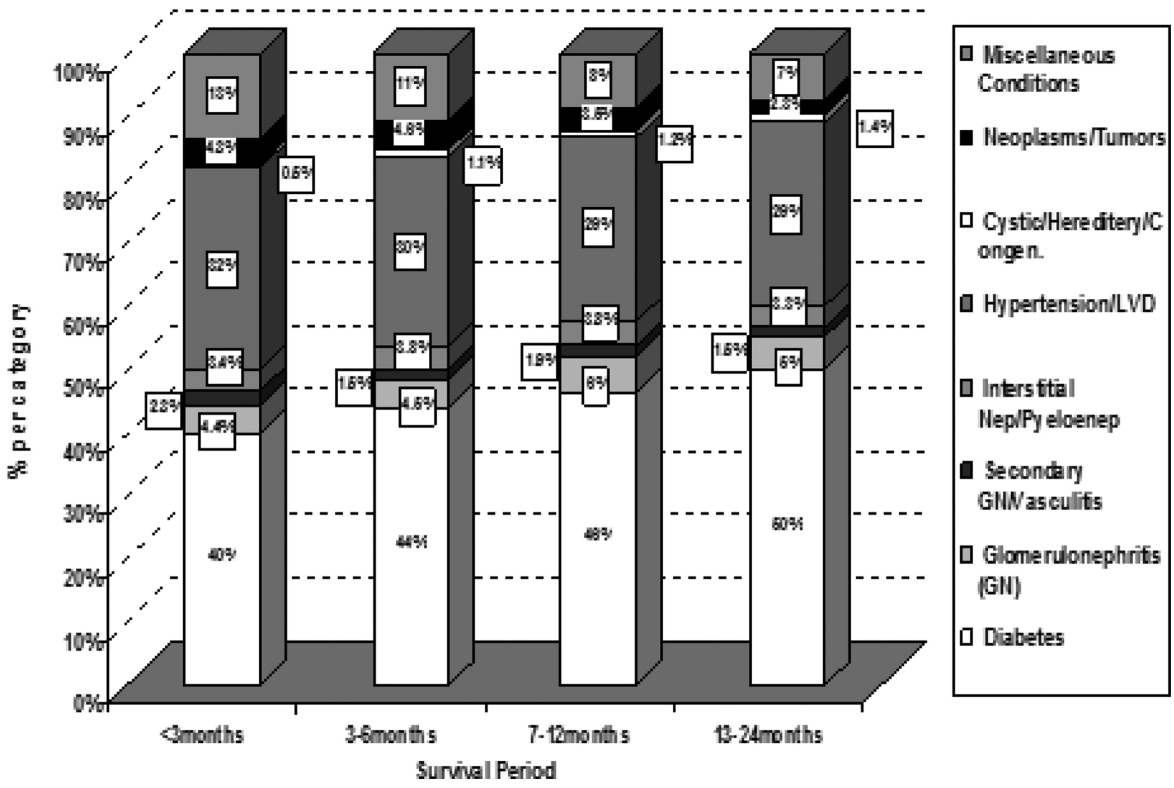

Figure 2.

Primary causes of ESRD for incident hemodialysis patients who died within 24 months after dialysis initiation from 5 year DaVita Cohort 07/01-06/06; N= 6,507

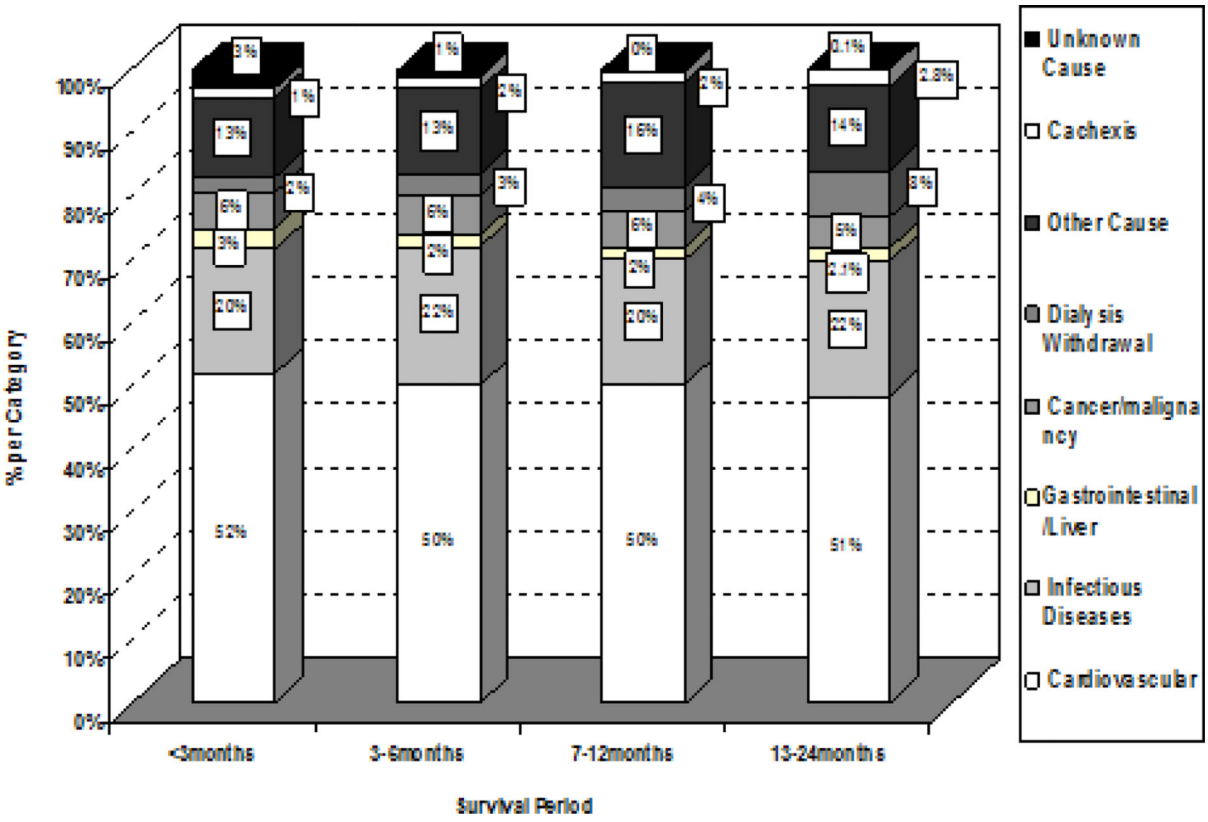

Figure 3.

Causes of death by the mortality periods for incident hemodialysis patients from 5 year DaVita cohort, excluding pts with missing causes of death; N=5,026 (1841 deaths that occurred after month 24 and 2,236 cases with no documented cause of death were excluded)

Table 1

Comparing patient characteristics across selected morality periods of the first 24 months in 18,702 incident hemodialysis patients who started dialysis therapy during 07/01/2001-06/30/2006 in a DaVita clinic

	Patients who died during the first 24 months				Survived >=2 years	p-value
	1-3 mo	4-6 mo	7-12 mo	13-24 mo		
N	n=1,994	n=1,271	n=1,550	n=1,851	n=12,041	
Age	72±13	70±13	69±13	69±13	60±15	<.0001
Gender (% female)	45%	47%	47%	44%	44%	0.16
Diabetes mellitus (%)	50%	57%	58%	61%	53%	<.0001
Race (%)						
White	62%	57%	60%	58%	47%	<.0001
Black	20%	24%	21%	22%	27%	<.0001
Hispanic	12%	11%	11%	12%	15%	<.0001
Other	6%	8%	8%	8%	11%	<.0001
Primary insurance (%)						
Medicare	65%	68%	70%	69%	51%	<.0001
Medicaid	5%	7%	7%	4%	6%	0.06
Other	30%	25%	13%	12%	43%	<.0001
Marital Status (%)						
Married	49%	46%	47%	54%	54%	<.0001
Divorced	5%	7%	7%	6%	7%	0.21
Single	21%	22%	20%	21%	26%	<.0001
Widowed	25%	25%	26%	19%	13%	<.0001
Kt/V (dialysis dose)	1.36±0.4	1.41±0.4	1.42±0.4	1.40±0.4	1.39±0.4	0.01
Vascular Access						
Dialysis Catheter (%)	81%	74%	65%	58%	53%	<.0001
AVF	8%	12%	16%	21%	30%	<.0001
Graft	11%	14%	19%	21%	17%	<.0001
Co-morbid Conditions (%)						
AIDS	0.6%	1%	0.7%	0.7%	0.4%	0.02
Cancer	9%	8%	7%	6%	4%	<.0001
Atherosclerotic Heart Disease	32%	27%	28%	27%	17%	0.005
Heart Failure	41%	37%	35%	33%	20%	<.0001
Pulmonary Disease COPD	12%	8%	9%	8%	4%	<.0001
Cerebro-vascular disease CVA	11%	11%	10%	11%	6%	<.0001
History of Hypertension	73%	74%	75%	79%	81%	0.04
Other Heart Diseases	%	10%	7%	7%	5%	<.0001
Non-ambulatory	10%	7%	5%	5%	2%	<.0001
Peripheral Vascular Disease PVD	17%	18%	17%	16%	9%	<.0001
HIV	0.8%	0.6%	1%	2%	0.3%	0.15

	Patients who died during the first 24 months				Survived >=2 years	p-value
	1-3 mo	4-6 mo	7-12 mo	13-24 mo		
Smoker	4%	4%	5%	5%	4%	0.17
Serum levels						
Albumin (g/dL)	3.1±0.6	3.3±0.5	3.3±0.5	3.4±0.5	3.6±0.5	<.0001
Albumin (% <3.5 g/ml)	72%	63%	56%	48%	35%	<.0001
Creatinine (mg/dL)	5.6±2.4	5.6±2.3	5.7±2.5	5.6±2.3	6.6±2.7	<.0001
TIBC (mg/dL)	193±63	205±58	214±57	222±51	232±50	<.0001
Bicarbonate (mg/dL)	22.6±4	22.6±4	22.6±4	22.4±4	22.0±4	<.0001
Phosphorus (mg/dL)	4.9±1.7	5.0±1.6	5.0±1.5	5.1±1.5	5.3±1.4	<.0001
Calcium (mg/dL)	8.7±0.8	8.8±0.8	8.8±0.8	8.7±0.8	8.9±0.8	<.0001
Ferritin (ng/mL)	549±749	419±522	374±490	314±365	278±347	<.0001
ISAT (%)	24±15	23±11	23±11	23±11	23±10	0.01
ALKP (u/L)	151±149	135±106	123±82	116±832	109±78	<.0001
PTH (pg/dl)	349±340	381±365	407±417	411±373	469±419	<.0001
nPCR (g/kg/day)	0.88±0.3	0.84±0.3	0.85±0.3	0.86±0.3	0.88±0.3	<.0001
nPCR (% >1 g/kg/day)	27%	24%	24%	25%	27%	0.0400
Blood hemoglobin (g/dL)	10.5±1.5	10.7±1.4	10.8±1.4	10.9±1.4	11.0±1.4	<.0001
Hemoglobin (% <10 g/dl)	24%	31%	29%	25%	24%	<.0001
WBC ($x10^3$/ vl)	9.5±5.6	8.3±3.1	8.2±3.1	7.9±2.9	7.7±2.5	<.0001
Lymphocyte (% of WBC)	14±7.6	16±7.1	17±7.1	18±7.2	19.±7.4	<.0001
EPO dose (units q HD)	9817±5844	9752±5231	9385±5040	9038±5155	9031±5081	<.0001
Paricalcitol dose (mcg./HD)	3.8±3.1	3.8±3.0	3.6±3.0	3.7±3.3	3.9±3.4	0.07
BMI (kg/m2)	25.7±9	25.5±7	26.1±7	26.4±7	28.2±7	<.0001
eGFR (ml/min)	11.4±5	10.9±4	10.8±5	10.8±5	9.6±3	<.0001
eGFR (% <10)	39%	52%	58%	51%	39%	<.0001
eGFR (% <15)	10%	16%	18%	16%	10%	<.0001

Table 2

Case-mix adjusted death hazard ratios for the association between mortality at different time periods and individual predictors for incident hemodialysis patients in18,707 incident hemodialysis patients. Note that deaths and person-times before and/or after each period are censored.

	<3 mo	**4-<6 mo**	**7-<12 mo**	**13-<24 mo**
Predictor	HR 95% CL	HR 95% CL	HR 95% CL	HR 95% CL
Age (decades)	1.50 (1.43-1.56)	1.44 (1.35-1.54)	1.32 (1.26-1.38)	1.33 (1.28-1.39)
Gender (female vs. male)	1.00 (0.90-1.11)	0.95 (0.83-1.09)	0.89 (0.79-1.01)	0.95 (0.85-1.05)
Diabetes mellitus	0.86 (0.78-0.94)	0.95 (0.84-1.07)	1.03 (0.93-1.15)	1.11 (1.00-1.23)
Race				
Whites vs. Blacks	1.12 (0.97-1.28)	1.01 (0.86-1.18)	1.33 (1.16-1.52)	1.29 (1.14-1.46)
Whites vs. Hispanics	1.09 (0.94-1.27)	1.24 (1.02-1.52)	1.53 (1.23-1.85)	1.33 (1.14-1.56)
Whites vs. Others	1.40 (1.15-1.70)	1.18 (0.93-1.49)	1.43 (1.17-1.75)	1.48 (1.23-1.77)
Health Insurance				
Medicaid vs. Medicare	1.48 (1.17-1.87)	1.74 (1.32-2.29)	1.68 (1.30-2.18)	1.07 (0.84-1.37)
Other vs. Medicare	1.10 (0.93-1.31)	0.90 (0.77-1.05)	0.78 (0.66-0.91)	0.78 (0.69-0.89)
Marital status				
Divorced vs. Married	0.90 (0.60-1.33)	1.09 (0.67-1.80)	1.15 (0.69-1.92)	0.86 (0.60-1.25)
Single vs. married	1.39 (1.16-1.65)	1.33 (1.10-1.60)	1.19 (0.94-1.51)	1.08 (0.88-1.34)
Widowed vs. Married	1.12 (0.87-1.45)	1.25 (0.83-1.88)	1.46 (1,08-1.97)	1.00 (0.82-1.21)
KTV (0.2↓)	0.92 (0.88-0.96)	0.96 (0.93-1.00)	0.99 (0.92-1.03)	0.98 (0.95-1.01)
Vascular access				
CVC vs. AVF	2.99 (2.49-3.59)	2.46 (1.89-3.20)	2.06 (1.76-2.40)	1.63 (1.39-1.91)
CVC vs. Graft	2.48 (1.94-3.17)	1.84 (1.40-2.40)	1.43 (1.21-1.69)	1.34 (1.15-1.55)
CVC vs. AVF+Graft	2.66 (2.27-3.11)	2.22 (1.81-2.72)	1.80 (1.53-2.12)	1.52 (1.37-1.69)
BMI (2kg/m2)	0.92 (0.90-0.94)	0.93 (0.91-0.95)	0.94 (0.92-0.96)	0.92 (0.91-0.94)
Co-morbidities				
Cardiac disorders				
Atherosclerotic Heart D	1.09 (0.97-1.23)	0.96 (0.83-1.11)	1.04 (0.92-1.18)	1.05 (0.93-1.18)
Heart Failure	1.31 (1.11-1.54)	1.36 (1.20-1.55)	1.29 (1.15-1.45)	1.33 (1.19-1.48)
Other cardiac disease	1.23 (1.05-1.44)	1.45 (1.20-1.76)	1.02 (0.83-1.25)	1.00 (0.82-1.22)
Vascular/Pulmonary				
CVA	1.07 (0.92-1.24)	1.09 (0.91-1.31)	1.08 (0.91-1.28)	1.27 (1.09-1.48)
PVD	1.11 (0.98-1.27)	1.27 (1.08-1.49)	1.28 (1.10-1.49)	1.16 (1.01-1.33)
COPD	1.43 (1.23-1.67)	1.02 (0.82-1.27)	1.14 (0.94-1.37)	1.13 (0.95-1.36)
Other co-morbidities				
Cancer	1.31 (1.11-1.54)	1.36 (1.11-1.67)	1.30 (1.06-1.60)	1.15 (0.95-1.40)
Non-ambulatory	2.01 (1.70-2.38)	1.73 (1.38-2.18)	1.46 (1.15-1.84)	1.66 (1.33-2.09)
Smoking	0.93 (0.73-1.18)	1.13 (0.86-1.50)	1.29 (1.02-1.63)	1.14 (0.91-1.43)
Hypertension	0.74 (0.67-0.82)	0.72 (0.63-0.82)	0.71 (0.63-0.80)	0.82 (0.73-0.92)

	<3 mo	4-<6 mo	7-<12 mo	13-<24 mo
Lab parameters				
Albumin (0.2g/dl ↓)*	1.21 (1.18-1.24)	1.17 (1.15-1.20)	1.15 (1.13-1.18)	1.12 (1.10-1.14)
Albumin <3.5 g/ml*	2.56 (2.30-2.84)	2.04 (1.81-2.31)	1.89 (1.70-2.10)	1.59 (1.44-1.75)
Hemoglobin (1 g/dl ↓)*	1.24 (1.20-1.28)	1.13 (1.09-1.18)	1.07 (1.03-1.11)	1.05 (1.01-1.08)
Hemoglobin <10 g/ml	1.58 (1.33-1.74)	1.37 (1.21-1.55)	1.25 (1.11-1.49)	1.11 (0.99-1.24)
Creatinine (mg/dl ↓)*	1.03 (1.01-1.06)	1.04 (1.01-1.07)	1.03 (1.00-1.05)	1.05 (1.03-1.08)
Ca (mg/dl)*	1.14 (1.07-1.22)	1.09 (1.00-1.18)	1.11 (1.04-1.19)	1.03 (0.97-1.09)
Phosphorous (mg/dl)*	1.06 (1.02-1.10)	1.03 (0.99-1.08)	1.04 (1.00-1.09)	1.01 (0.97-1.05)
nPCR (0.2g/kg/day)	1.08 (1.03-1.13)	0.94 (0.89-1.00)	0.93 (0.89-0.97)	0.96 (0.92-1.00)
nPCR >1.0 g/kg/day	1.21 (1.06-1.38)	0.96 (0.8-1.14)	0.89 (0.74-1.07)	0.99 (0.87-1.13)
WBC (5000/HPF ↑)	1.52 (1.45-1.59)	1.26 (1.15-1.39)	1.26 (1.16-1.37)	1.14 (1.04-1.25)
Lym (10%)*	1.87 (1.70-2.05)	1.42 (1.31-1.55)	1.33 (1.24-1.44)	1.17 (1.09-1.26)
TIBC (50g/dl)*	1.51 (1.43-1.59)	1.40 (1.31-1.49)	1.30 (1.22-1.38)	1.20 (1.14-1.26)
Ferritin (500* ng/dl)	1.24 (1.20-1.28)	1.23 (1.18-1.29)	1.27 (1.21-1.33)	1.20 (1.14-1.28)
PTH (100pg/ml)	0.96 (0.94-0.97)	0.97 (0.95-0.99)	0.99 (0.97-1.01)	0.99 (0.97-1.01)
ISAT (10%)	1.09 (1.05-1.13)	1.05 (0.99-1.11)	1.02 (0.98-1.08)	1.07 (1.02-1.13)
eGFR (each 1 inc)	1.03 (1.02-1.04)	1.01 (1.00-1.03)	1.01 (1.00-1.03)	1.03 (1.02-1.04)
eGFR <10	1.29(1.17-1.42)	1.20 (1.07-1.35)	1.04 (0.94-1.16)	1.11 (0.97-1.28)
eGFR <15	1.43 (1.27-1.60)	1.09 (0.93-1.28)	1.29 (1.12-1.48)	1.02 (0.83-1.24)

* Indicates decrease per unit change of serum level of laboratory parameter

Table 3

Case-mix adjusted death hazard ratios (95% confidence interval (CI)) for the association between CV and infection-related mortality at different time periods and several individual predictors for incident hemodialysis patients in18,707 incident hemodialysis patients. Note that deaths and person-times before and/or after each period are censored.

	Deaths 0-3 months	**Deaths 4-6months**	**Deaths 7-12months**	**Deaths 13-24months**
Predictor Outcome 1: CV mortality Outcome 2: Infectious mortality	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Whites vs. Blacks				
CV mortality	1.14 (0.92 - 1.41)	1.02 (0.81 - 1.30)	1.20 (0.94 - 1.54)	1.46 (1.18 - 180)
Infectious mortality	1.26 (0.85 - 1.89)	1.28 (0.84 - 1.96)	1.70 (1.12 - 2.58)	1.20 (0.85 - 1.70)
Whites vs. Hispanics				
CV mortality	1.28 (0.98 - 1.66)	1.16 (0.84 - 1.62)	1.75 (1.28 - 2.39)	1.60 (1.22 - 2.10)
Infectious mortality	0.91 (0.60 - 1.37)	1.38 (0.42 - 2.33)	3.43 (1.76 - 6.69)	1.58 (0.96 - 2.62)
Heart Failure				
CV mortality	1.68 (1.41 - 1.99)	1.74 (1.42 - 2.14)	1.86 (1.53 -2.24)	1.43 (1.20 - 1.71)
Infectious mortality	1.56 (1.14 - 2.14)	1.76 (1.24 - 2.50)	1.17 (0.80 - 1.70)	1.69 (1.24 - 2.31)
CVC vs. AVF+Graft				
CV mortality	2.45 (1.74 - 3.44)	2.09 (1.57 - 2.80)	1.58 (1.31 - 1.93)	1.59 (1.30 - 1.97)
Infectious mortality	3.32 (2.14 - 5.16)	4.03 (2.66 - 6.09)	2.23 (1.50 - 3.32)	1.74 (1.23 - 2.47)
Albumin <3.5 vs. >3.5				
CV mortality	2.15 (1.81 - 2.55)	1.89 (1.54 - 2.33)	1.83 (1.53 - 2.19)	1.80 (1.53 - 2.11)
Infectious mortality	4.92 (3.45 - 7.00)	3.21 (2.23 - 4.62)	2.34 (1.65 - 3.30)	1.48 (1.09 - 2.01)

CVC - central venous catheter; AVF - arteriovenous fistula; graft - arteriovenous graft